Remarks

Claims 1, 3, 11 and 27-37 are pending in the subject application. No claims have been amended, added or cancelled herein.

35 U.S.C. § 102(b) Rejection

Claims 1, 3, 11, 27 and 29-32 were rejected under 35 U.S.C. §102(b) as anticipated by WO 01/64749 ("Kloetzer"). This rejection is respectfully traversed.

Kloetzer prophetically describes the use of an MIF antibody for treating arthritis, psoriasis, glomerulonephritis, septic shock, atopic dermatitis, and retinopathy associated with diabetes or lupus. Kloetzer does not teach a method of inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes, as set forth in Claims 1, 3, 11, 27, 34 and 35, or a method of inhibiting the development of type 1 diabetes in a mammal at risk for type 1 diabetes, as set forth in Claims 29-33, 36 and 37.

Applicant has previously asserted that diabetic retinopathy is not type 1 diabetes. A claim is not anticipated unless the identical invention is disclosed. See MPEP §2131.02: " 'The identical invention must be shown in as complete detail as is contained in the ... claim.' Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." Whilst the Office Action asserts that "diabetic retinopathy most certainly is an aspect of type 1 diabetes," what is relevant in a 35 U.S.C. §102(b) rejection is does the cited reference teach the exact method claimed, i.e., in relevant part, "A method of inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes." However, while the complication known as diabetic retinopathy can occur in some diabetes patients, it does not exist in all diabetes patients. Moreover, diabetic retinopathy can occur *without* diabetes, as supported by "American Diabetic Association Scientific Sessions: Retinopathy Found in Pre-Diabetes" submitted herewith by EFS. This underlines the fact that the complication diabetic retinopathy is not diabetes.

Accordingly, applicant maintains that the anticipation rejection is improper and respectfully request that the Examiner reconsider and withdraw this rejection.

35 U.S.C. § 103(a) Rejection

Bojunga in view of Nishihira & Ogata

Claims 1, 3, 11, 27, and 29-32 were rejected under 35 U.S.C. §103(a) as unpatentable over Bojunga et al. ("Bojunga") in view of Nishihira and Ogata ("Nishihira"). This rejection is respectfully traversed.

The rejection is premised on the assertion that Bojunga teaches treatment of diabetes with an MIF inhibitor. Nishihira is cited for the notion that anti-MIF antibodies and small organic molecules are interchangeable.

Bojunga does not teach treatment of diabetes. Instead, Bojunga (i) experimentally induces diabetes and looks at the accompanying MIF nucleic acid levels and (ii) determines that MIF-mRNA expression was elevated in the splenic lymphocytes of NOD mice in which diabetes spontaneously occurred.

As pointed out by applicant with the previous submission of the article Greenbaum et al., the art makes it clear it is not reasonably predictable whether raised mRNA levels are correlated with raised levels of the encoded protein. To quote Greenbaum et al., "Attempts to correlate protein abundance with mRNA expression levels have had variable success." Applicant has also previously provided, in the form of Ogata et al., a specific example for the relevant protein, MIF, where high MIF mRNA expression was not positively correlated with high MIF protein levels[1]. Bojunga hypothesized as to why this may be the case, but that still does not amount to a

[1] Whilst the Final Office Action asserts that "this can easily be explained by either secretion or degradation of the protein" other possible explanations include the failure, inhibition or regulation of one or more steps between transcription and translation. In any event, all of these possibilities underline the unpredictability of the relationship between mRNA levels and encoded protein levels and that it is not predictable that raised MIF mRNA levels *in vivo* correlates with raised MIF protein levels.

reasonable predictability. The Office Action emphasizes that, in Ogata, expression did not correlate in only a single cell type. However, only two cell types were tested, and no correlation was found in one type. In Bojunga, the primary reference, one cell type was tested and no correlation was found.

Thus, in light of Ogata, Bojunga and Greenbaum, MIF protein levels are not reasonably predictable from MIF mRNA levels. This is significant, because the rejection over the primary reference Bojunga is based on the concept that increased MIF protein levels increases diabetes incidence. Bojunga states, however, that the correlation between diabetes incidence in the test mice (i.e. NOD mice which are susceptible to spontaneous development of autoimmune diabetes) and *exogenously* added MIF, though positive, was not statistically significant.

Moreover, the notion that MIF RNA levels observed in Bojunga could be reasonably predictive of MIF protein levels *in vivo* is clearly incorrect (based on Bojunga, Ogata and Greenbaum as explained above). Furthermore, Bojunga does not demonstrate that MIF protein levels are raised during diabetes. Instead, Bojunga shows that diabetes is experimentally associated, at a statistically non-significant level, with intraperitoneal administration of exogenous recombinant MIF. As summarized by Bojunga in the Abstract "our preliminary study suggests a possible role of MIF in autoimmune inflammatory events." Bojunga's speculation on "possible" role for MIF in type-1 diabetes is couched in language which points to the unpredictability of any related therapeutic strategy. In addition, the strategy is not specified - for example, is the therapy a manipulation of MIF mRNA levels?

Nishihira is cited in the Office Action in combination with Bojunga for the notion that "small organic molecules are interchangeable with antibodies in the context of treatment of autoimmune disease." The Perspectives section of Nishihira is identified as the source of this assertion. However, the only sentence in the Perspectives section

regarding antibodies states "the therapeutic use of anti-MIF antibodies and small molecules inhibiting MIF activity could be promising for septic shock...". There is no statement or implication for the notion of interchangeability here. If there is support for such a notion in Nishihira, applicant requests that the Examiner point out the support by page number and position so that they may better respond to this assertion. Otherwise, applicant requests that this assertion of "interchangeability" be withdrawn as it is appears to have no actual basis in the cited art.

Thus, Bojunga do Nishihira do not teach or suggest the invention as claimed, and the differences between the cited art and the claimed invention are not obvious (MPEP 2141 (III)). Accordingly, applicant respectfully request that the Examiner reconsider and withdraw this rejection.

Bojunga in view of Nishihira and U.S. Patent No. 5,530,101

Claims 28 and 33 were rejected under 35 U.S.C. §103(a) as unpatentable over Bojunga in view of Nishihira as applied to Claims 1, 3, 11 and 27 above, and further in view of U.S. Patent No. 5,530,101 ("Queen"). The asserted teachings of Bojunga and Nishihira are described above, and Queen is cited for the notion of humanized monoclonal antibodies. This rejection is respectfully traversed.

As discussed above, the claimed invention is patentable over Bojunga in view of Nishihira because of the unpredictability and for the lack of teaching or suggesting of all the elements of the claim (the differences not being obvious; MPEP 2141 (III)). The addition of Queen does not remedy the failure of Bojunga and Nishihira to render the claimed method obvious. More specifically, Queen was cited for describing the production of humanized antibodies but Queen suggests nothing that would render the claimed method, regarding the use of MIF antibodies for inhibiting progress or development of type 1 diabetes, obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

WO 01/32606 and Nishihira

Claims 1, 3, 11, 27 and 29-32 were rejected under 35 U.S.C. §103(a) as unpatentable over WO 01/32606 in view of Nishihira as cited above. This rejection is respectfully traversed.

WO 01/32606 describes small molecules having MIF antagonist activity and suggest that the compounds can be used for the treatment of inflammatory disorders. However, WO 01/32606 does not provide any data showing any of its compounds are indeed useful for inhibiting the progress of type 1 diabetes in a subject having type 1 diabetes, or can be used to inhibit the development of type 1 diabetes in a subject at risk for type 1 diabetes. Furthermore, with respect to MIF antibodies, WO 01/32606 teaches that "such biological agents, unfortunately, have certain limitations with regard to their clinical utility. Therefore there is a need in the art to discover and develop small organic molecules that function as MIF antagonists..." (WO 01/32606, page 2). The Office Action states, in response to applicant previously pointing this out, that "Said single sentence hardly comprises a persuasive teaching of any sort." To clarify applicant's position, it is noted that WO 01/32606 is being cited for the notion of treating an inflammatory disease with an anti-MIF agent, yet WO 01/32606 states antibodies have limited clinical utility and that "Therefore there is a need in the art to discover and develop small organic molecules." All of the remaining pages of the publication do not refer to antibodies and instead regard non-antibody small molecules (Schiff base condensation products) to fulfill that stated need. Clearly, one skilled in the art, reading WO 01/32606 and without using impermissible hindsight, would consider WO 01/32606 as teaching away from anti-MIF antibodies and instead using anti-MIF small molecules which are the reason for WO 01/32606. Moreover, if, indeed, a "single sentence hardly comprises a persuasive teaching of any sort", and what the sentence asserts is that antibodies are deficient, the sentence certainly cannot be asserted for the *opposite* notion - that antibodies would be selected.

The non-obviousness of the claimed method in view of the teaching away from using an MIF antibody for therapeutic use is not remedied by Nishihira which describes the use of MIF as a target molecule in multiple sclerosis, not type 1 diabetes.

For these reasons, the claimed invention is not obvious over WO 01/32606 and Nishihira. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

WO 01/32606 in view of Nishihira and Queen

Claims 28 and 33 were rejected under 35 U.S.C. §103(a) as being unpatentable over WO 01/32606 in view of Nishihira. This rejection is respectfully traversed.

As discussed above, the claimed invention is patentable over WO 01/32606 and Nishihira. The addition of Queen does not remedy the failure of Bojunga and Nishihira to render the claimed method obvious. More specifically, Queen was cited for describing the production of humanized antibodies but Queen suggests nothing that would render the claimed method, regarding the use of MIF antibodies for inhibiting progress or development of type 1 diabetes, obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Applicant	:	Yousef Al-Abed
Appl. No.	:	10/594,641
Filed	:	March 28, 2008

Information Disclosure Statement

The Examiner indicated that certain previously submitted information on form PTO/SB/08b was not considered. In this regard, applicant is submitting herewith a new PTO/SB/08b addressing the issues enumerated on the PTO/SB/08b returned to applicant with the current Office Action.

In regard to the International Report on Patentability for related Application No. PCT/US2005/010521, published April 24, 2007, Simin Baharlou, applicant has revised description of said item on the PTO/SB/08b submitted herewith and notes that the item is 5 pages and is available in the IFW dated 3.28.2007.

Applicant requests that the Examiner consider the items listed thereon and return a copy of the enclosed PTO/SB/08b indicating the items have been considered.

Applicant : Yousef Al-Abed
Appl. No. : 10/594,641
Filed : March 28, 2008

Conclusion

No fee is deemed necessary in connection with the filing of this Communication. If any is required to preserve the pendency of the subject application, authorization is hereby given to charge any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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